# Early Detection and Management of Prader-Willi Syndrome in Egyptian Patients

Hala T. El-Bassyouni[1] Nagwa Hassan[2] Inas Mahfouz[2] Azza E. Abd-Elnaby[3] Mostafa I. Mostafa[4] Angie M.S. Tosson[5]

[1] Department of Clinical Genetics, National Research Centre, Cairo, Egypt
[2] Department of Nutrition, National Research Centre, Cairo, Egypt
[3] Department of Human Cytogenetics, National Research Centre, Cairo, Egypt
[4] Department of Oro-dental Genetics, National Research Centre, Cairo, Egypt
[5] Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt

**Address for correspondence** Hala T. El-Bassyouni, PhD, Department of Clinical Genetics, National Research Centre, El-Tahreer Street, Cairo 12622, Egypt (e-mail: halabassyouni@yahoo.com).

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## Abstract

Prader-Willi syndrome (PWS) is a distinct neurodevelopmental disorder associated with the deletion within the chromosomal 15q11-q13 region or uniparental disomy of chromosome 15. The etiologic heterogeneity of PWS makes it very difficult to establish uniform diagnostic methods which would result in the detection of most affected individuals. The objective was to report the clinical criteria and oro-dental features in PWS, to report the effect of diet and laser acupuncture on PWS and highlighted an easy effective method for early diagnosis of individuals with PWS. The study included seventeen cytogenetically proven individuals with Prader-Willi syndrome. These patients were subjected to meticulous history taking, clinical examination including oro-dental examination, bone densitometry and neuropsychiatric evaluation. They received laser acupuncture sessions in addition to nutrition intervention. All cases had characteristic facies, hypotonia and various psychosocial difficulties. Other criteria of PWS were present in different percentages. Karyotyping revealed deletion 15q11-q13 in 6 patients, and fluorescence in situ hybridization (FISH) revealed a microdeletion in 15q11–q13 in the other 11 patients. To our knowledge, partial ankyloglossia, median grooved tongue and hypodontia have not previously been reported in PWS patients. Laser acupuncture sessions and diet were effective in weight decline for PWS patients. Our study emphasizes the importance of early detection of PWS, laser sessions, diet restriction and oro-dental examination in the follow up of patients with Prader Willi syndrome.

**Keywords**
- early PWS detection
- management
- oro-dental findings
- PWS diagnostic strategy
- weight loss

## Introduction

Prader-Willi syndrome (PWS; MIM 176270) is a genetic multisystem disorder, which is caused by the absence of paternally expressed critical region within chromosome 15q11-q13.[1] Most cases of Prader-Willi syndrome (65–70%) result from deletion of a critical region within the paternally inherited 15q11-q13.[2] Maternal uniparental disomy, triggered by chromosomal nondisjunction, causes 20–30% of PWS. Fewer than 3% of patients have mutations in the imprinting center, which carries a risk of recurrence.[3] Clinically PWS has two distinct phases. The first is from birth till around 2 years of age. This phase is characterized by feeding problems and variable degrees of neonatal non progressive

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hypotonia. The second phase starts by the appearance of hyperphagia around the age of 2 years. The foremost clinical features of PWS include neonatal hypotonia, feeding difficulty, characteristic facial features (e.g., narrow bifrontal diameter, almond-shaped eyes, upward slanting palpebral fissures, strabismus, full checks, small mouth, down-turned corners of the mouth, thin upper lip), small hands and feet, developmental delay, hypopigmentation of skin and hair, hypogonadism, and hyperphagia-caused obesity.[4] The facial features are present in the two phases but become more obvious in the second phase. Social aggression, anxiety, skin-picking, symptoms of inattention, impulsivity, and oppositionality are associated psychosocial problems.[5] Oro-dental features are rarely mentioned in the literature. Triangular mouth, delayed tooth eruption, enamel hypoplasia, malocclusion, rampant caries, excessive tooth wear, localized periodontal involvement and decreased salivation are the common previously reported findings.[6,7] PWS is the most frequent cause of syndromic obesity and occurs in 1 in 25,000 live births.[4] It was shown that early PWS diagnosis can prevent obesity. In this respect, individuals with PWS have a higher fat mass than is generally seen in simple obesity with the same degree of weight excess, both in children and in adults.[8] Patients with PWS generally die from complications related to obesity, including type 2 diabetes mellitus (DM2), arterial hypertension, sleep apnea, respiratory insufficiency and cardiovascular disease.[9] Laser acupuncture application in obesity increases the excitability of the satiety center in the hypothalamus, and also raises the serotonin levels both of which have been shown to increase tone in smooth muscle of the stomach and thus suppressing appetite.[10,11] The aim of this study is to report the clinical criteria and oro-dental features in PWS and to report the effect of diet and laser acupuncture on PWS. We also highlighted an easy and effective method for early diagnosis of individuals with PWS.

## Patients and Methods

The study started in May 2017 and included 25 patients with provisional diagnosis of PWS. They were recruited from the Clinical Genetics Department, National Research Centre, Egypt and Abou Elreesh Children Hospital, Cairo University, Egypt. Cytogenetic studies including karyotyping and Fluorescence In Situ Hybridization (FISH) which confirmed that 17 patients had PWS. The PCR-based methylation test (PBMT) for 15q11-q13 was not available to diagnose the remaining 8 suspected PWS cases. Therefore, only the 17 cytogenetic proven patients were included in this study. Diagnosis of PWS depends on the neonatal history, characteristic clinical features followed by chromosomal and Fluorescence In-Situ Hybridization (FISH) analysis. FISH was performed on metaphase spread from peripheral blood according to modification of Pinkel et al,[12] and manufacturer's instructions by using locus-specific probe (LSI) Prader-Willi SNRPN (15q11) supplied by Kreatech Diagnostics (United Kingdom). Complete clinical examination including meticulous neonatal and childhood history, pedigree analysis, developmental assessment, behavioral assessment, oro-dental examination, nutritional evaluation and bone mineral density (BMD) evaluation were conducted for all patients. All parents supplied photos of the children during infancy and early childhood. The development was assessed using the Arabic version of the Revised Wechsler Intelligence Scale for children.[13] Neuropsychiatric evaluation by a pediatric/adult neurologist (according to the patient's age) and a psychiatrist was performed to detect various psychological abnormalities. The PWS patients received at least 10 laser acupuncture sessions in the Acupuncture and Laser clinic of the Centre of Excellence for Medical Research, National Research Centre as well as diet regulations from 6 months. A cold laser beam by diode semiconductor (Aluminum Gallium) laser device was used for 1 minute on each point. Its power was 100 mw and wavelength was 780 nm. The probe of the laser beam was applied perpendicularly on the skin at the points of obesity as follows: (G.V: 12, S.T: 25, S.T: 36, S.P: 6, S.P: 14, S.P: 15). According to the World Association of Laser Therapy (WALT) there is no maximum for the joules given by the cold semiconductor devices (year 2011). This research was reviewed and approved by the Research Ethics Committee at the National Research Centre according to "World Medical Association Declaration of Helsinki" in 1995 (as revised in Seoul 2008) and written consent was obtained.

## Results

The study comprised 17 cytogenetically proven PWS patients. There were 9 males and 8 females. Their ages ranged from 6–15 years (mean 9.82 $\pm$ 2.77). Decreased fetal movements were mentioned by 9 mothers. All patients had a history of infantile hypotonia. Feeding problems, which ranged from weak suck (9 cases) to oro- or nasogastric tube feeding for variable time periods (7 cases) were reported in 16 cases. Hypogonadism was found in 10 cases, where males showed micropenis, hypospadias and/or undescended testes; females had hypoplastic or absent labia minora and clitoris. Facial dysmorphism was present in all cases, where two to three facial features were detected during infancy from photos, while at least four facial features were found by examination. On examination patients presented with hypotonia, short stature, small hands and feet. Hypopigmentation was present in three patients. Small hands and feet were detected in all patients during examination and from their photos as infants. Four cases had sleep problems. All the above-mentioned criteria, in addition to previous reports of developmental delay at young age, were used to calculate the PWS diagnostic criteria according to Gunay-Aygun et al,[14] when children were 3 years of age or younger. Seventy-six percent (13/17) of our patients fulfilled the PWS criteria at 3 years of age or younger, while 94.1% (16/17) of the examined patients had the required score for diagnosis of PWS above 3 years. On examination the patients had variable degrees of hyperphagia and increased body weight. Developmental delay ranged from

**Table 1** Summary of clinical data

| No. | Age (y) | Sex | PWS Diagnostic Criteria | | | | | | | | | | | | | | | Bone mineral density |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Major criteria | | | | | | Minor criteria | | | | | | | | | |
| | | | Hypotonia | Neo. feeding prob. | Abn. Genitalia | Facies | DQ | Overweight/obesity | Hyperphagia | Decreased fetal movements | Sleep dist. | Skin hypo pig. | Small hands and feet | Eye | Oro-dental | Skin picking | Behavior problem | |
| 1 | 6 | M | + | + | + | + | + | + | + | + | − | − | + | al | + | − | + | N |
| 2 | 13 | F | + | + | + | + | + | + | − | − | + | − | + | − | + | − | + | N |
| 3 | 15 | F | + | + | − | + | + | + | + | + | − | − | + | al | + | − | + | N |
| 4 | 9 | F | + | + | + | + | − | + | + | − | − | + | + | al | + | − | + | N |
| 5 | 11 | M | + | + | + | + | − | + | + | NA | − | + | + | squ | + | − | + | N |
| 6 | 7 | M | + | + | + | + | ++ | + | − | + | − | − | + | al | + | − | + | N |
| 7 | 10 | M | ++ | + | − | + | + | + | + | NA | + | − | + | al | + | − | + | N |
| 8 | 12 | M | + | + | + | + | ++ | + | − | + | − | − | + | − | + | − | + | N |
| 9 | 7 | M | + | + | − | + | + | + | + | NA | − | + | + | − | + | − | + | N |
| 10 | 15 | F | + | − | − | + | + | + | + | NA | + | − | + | al | + | − | + | N |
| 11 | 10 | F | + | + | + | + | ++ | + | + | + | − | − | + | al, squ | + | − | + | Osteo-penia |
| 12 | 7 | F | + | + | − | + | ++ | + | + | + | − | − | + | − | + | − | + | N |
| 13 | 11 | M | + | + | + | + | + | + | − | + | − | − | + | al | + | − | + | N |
| 14 | 9 | F | + | + | − | + | − | + | + | NA | + | − | + | squ | + | − | + | N |
| 15 | 7 | F | + | + | + | + | − | + | + | + | − | − | + | squ | + | − | + | N |
| 16 | 8 | M | + | + | + | + | + | + | + | + | − | − | + | al | + | − | + | N |
| 17 | 10 | M | + | + | − | + | ++ | + | + | NA | − | − | + | al | + | − | + | N |

Abbreviations: Abn. Genitalia, abnormal genitalia; al, almond-shaped eyes; DQ, developmental quotient; F, female; hypotonia, the hypotonia was mainly neonatal (+) and one case had hypotonia (++) on examination; M, male; N, normal; NA, not available; Neo. feeding prob., neonatal feeding problems; sleep dist., sleep disturbances; squ., squint.

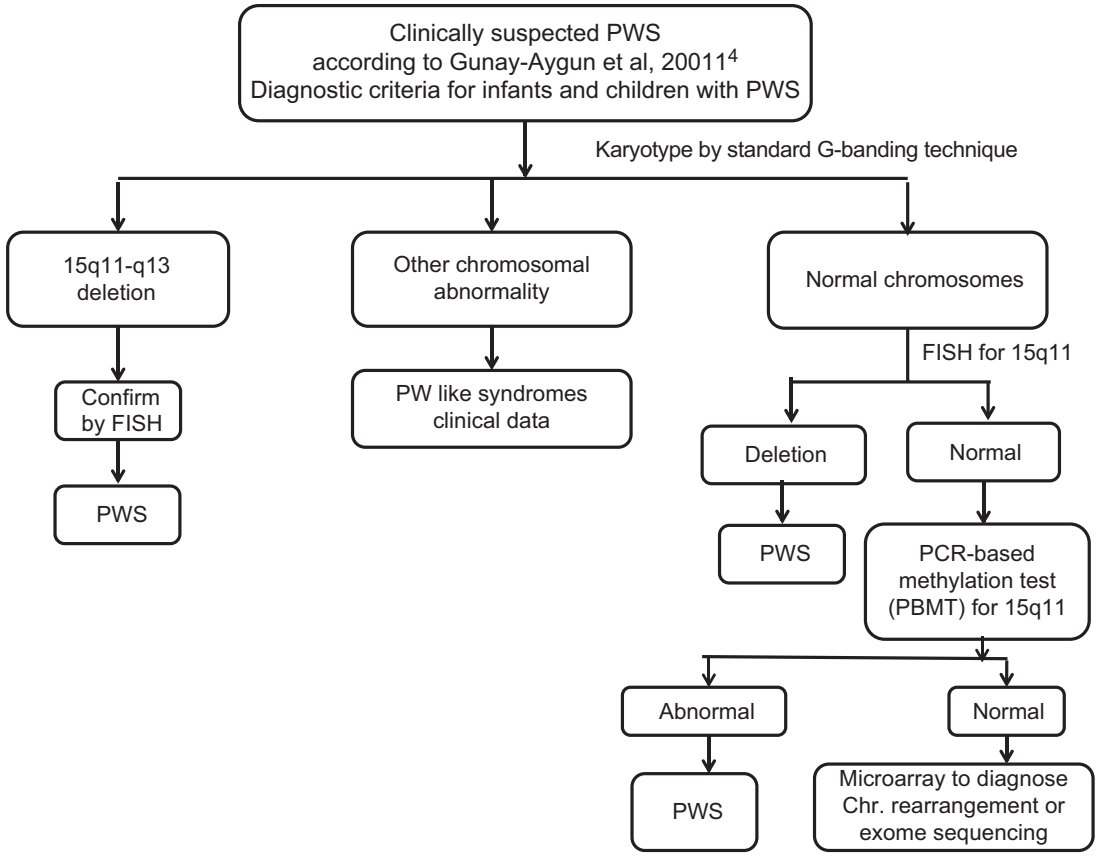


**Fig. 1** Flowchart elucidating the diagnostic approach to PWS cases. FISH, fluorescence in situ hybridization; PWS, Prader-Willi syndrome.

mild (+) to moderate (++) in 13 patients, seven of these patients had previous reports of delayed development at the age of 3 years or younger (cases 1, 3, 6, 7, 10, 12, 13). Psychosocial problems were present in all patients and included social aggression, hyperactivity, stubbornness and inattention. None of the patients showed skin picking. Bone densitometry was estimated in all patients and osteopenia was present in one patient. The clinical data of PWS patients are shown in ►**Table 1**. ►**Fig. 1** is a flowchart describing the diagnostic approach to PWS cases.

The oro-dental features of the studied cases are summarized in ►**Table 2**. Decreased salivation (according to the history and thick dried saliva at corners of the mouth), malocclusion, long philtrum, thick lips, everted lower lip, thick upper labial frenum and microstomia were the most common reported features.

Chromosomal analysis using G-banding technique revealed deletion 15q11-q13 in six patients (35.3%), while FISH revealed a critical microdeletion within 15q11–q13 in the other 11 patients.

The patients had excessive appetite therefore laser acupuncture sessions along with diet regulations for 6 months was recommended. Five PWS patients were drop-outs, while 12 patients were committed to the nutritional program. They received 10 to 12 laser acupuncture sessions with the diet regulations program for at least 6 months, which resulted in

**Table 2** Oro-dental Features of PWS Cases

| | |
|---|---|
| Decreased salivation | 17/17 |
| Malocclusion | 13/17 |
| Long philtrum | 13/17 |
| Thick lips | 12/17 |
| Everted lower lip | 9/17 |
| Thick upper labial frenum | 9/17 |
| Microstomia | 9/17 |
| Teeth attrition (wear) | 6/17 |
| Delayed eruption | 6/17 |
| Hypoplastic maxilla | 6/17 |
| Gingival pigmentation | 4/17 |
| Microdontia | 4/17 |
| Enamel hypocalcification | 3/17 |
| Tented upper lip (triangular mouth) | 3/17 |
| Enamel hypoplasia | 2/17 |
| Median grooved tongue | 2/17 |
| Partial ankyloglossia | 2/17 |
| Rampant caries | 2/17 |
| Abnormal shaped teeth | 2/17 |
| Hypodontia | 1/17 |

Abbreviations: PWS, Prader-Willi syndrome.

**Table 3** Nutritional Evaluation of PWS Children

| Case number | Age (y) | Sex | Weight initial (kg) | Weight after 6 mo (kg) | Weight loss (kg) | Number of sessions |
|---|---|---|---|---|---|---|
| 1 | 6 | Male | 48 | 40 | 8 | 10 |
| 2 | 13 | Female | 93.9 | 89.5 | 4.4 | 10 |
| 3 | 15 | Female | 95.2 | 91 | 4.2 | 10 |
| 5 | 11 | Male | 82 | 75 | 7 | 12 |
| 6 | 7 | Male | 68 | 63.5 | 4.5 | 12 |
| 7 | 10 | Male | 72.4 | 66.3 | 6.1 | 10 |
| 8 | 12 | Male | 80.2 | 73 | 7.2 | 10 |
| 9 | 7 | Male | 55 | 48 | 7 | 10 |
| 10 | 15 | Female | 93.1 | 86.7 | 6.4 | 10 |
| 11 | 10 | Female | 66.4 | 58.6 | 7.8 | 10 |
| 16 | 8 | Male | 57.3 | 52 | 5.3 | 10 |
| 17 | 10 | Male | 63 | 57 | 6 | 10 |

weight loss ranging from 4 to 8 kg. Nutritional evaluation of the children with PWS is summarized in ►**Table 3**.

## Discussion

Prader-Willi syndrome is a clinically well-described genetic syndrome. Cytogenetic and molecular diagnosis of PWS is available.[1] However, clinical identification of patients for testing is still a challenge, as many features of PWS are nonspecific, and other features are variable depending on the patients' age. In this study, sixty eight percent of the patients provisionally suspected to have PWS were proven to have the disease using cytogenetic analyses. The PCR-based methylation test (PBMT) for amplification of 15q11-q13 region is the best test for the detection of different etiological causes of PWS.[15] Unfortunately, the test was not available at the time of our research. However, cytogenetic analysis is essential before molecular testing to rule out chromosomal anomalies that give Prader-Willi like phenotypes, which are called Prader-Willi like syndromes (PWLS).[16] Researchers reported PWLS in different imbalances of chromosomes 1, 2, 3, 6, 10, 12, 14, and X.[17,18] It has been documented that cytogenetic analyses diagnose 65 to 70% of PWS cases that are caused by 15q11-q13 deletion,[2] which agrees with 68% obtained in this study.

The characteristic paraoral features in the form of long philtrum, everted lower lip, microstomia and tented upper lip (triangular mouth; ►**Fig. 2B**) could be attributed to facial and jaw muscle hypotonia similar to congenital myotonic dystrophy as suggested by Mashiach et al[19] and Hennekam et al.[20] Decreased salivation was a constant feature in all cases which was supported by Bailleul-Forestier who reported decreased salivation in more than 50% of both studied and previously reported cases.[7] Decreased salivation is considered one of the causative factors of rampant caries, while it aggravates enamel hypoplasia and enamel hypocalcification. The high concentrations of calcium and phosphate in saliva plays a fundamental role in maintaining the physical-chemical integrity of enamel by remineralization.[21] According to previous reports, to our knowledge, hypodontia, median grooved tongue, and partial ankyloglossia (►**Fig. 2A**, **C**, **D**) have not been previously reported in PWS. Partial ankyloglossia and median grooved tongue could be congenital defects linked to breast feeding difficulties of those patients.[22–24]

All studied PWS patients had infantile hypotonia and at least two PWS facial features during neonatal and early childhood period, while sixteen patients (94.1%) had feeding difficulties. At the time of examination all studied patients presented with hypotonia. Hypotonia is a fundamental diagnostic criterion for the diagnosis of PWS.[1,14]

More than half of our patients (58.8%) had hypogonadism. Angulo et al,[4] elucidated that hypogonadism is a major diagnostic criterion for PWS. PWS hypogonadism has generally been attributed to hypothalamic dysfunction.[25]

Thirteen of our 17 PWS patients (76.5%) had delayed developmental milestones ranging from mild to moderate delay. Similar data were reported by other researchers.[3,15,26] Psychosocial challenges are common in PWS, as documented by several studies.[27,28] All the studied patients had some psychosocial difficulties.

Hypopigmentation was present in 3 of 17 (17.6%) individuals in this study. Previous studies reported up to 48% of individuals with PWS have hypopigmentation, which was suggested to be related to 15q11-q13 deletion.[3,29]

Dysmorphic facial features of PWS have been described by many researchers.[30,31] Facial dysmorphism was present in all cases even during infancy, but facial features typical of PWS became more obvious in children.

One patient (5.9%) was detected to have osteopenia by bone density measurement. Nakamura and coworkers[32] documented that 33.8% of their adult PWS patients had osteoporosis and 27.7% had osteopenia. However, Bonfig et al,[33] stated that bone mineral density was normal in children with PWS, while it was reduced in adults with PWS. This finding may

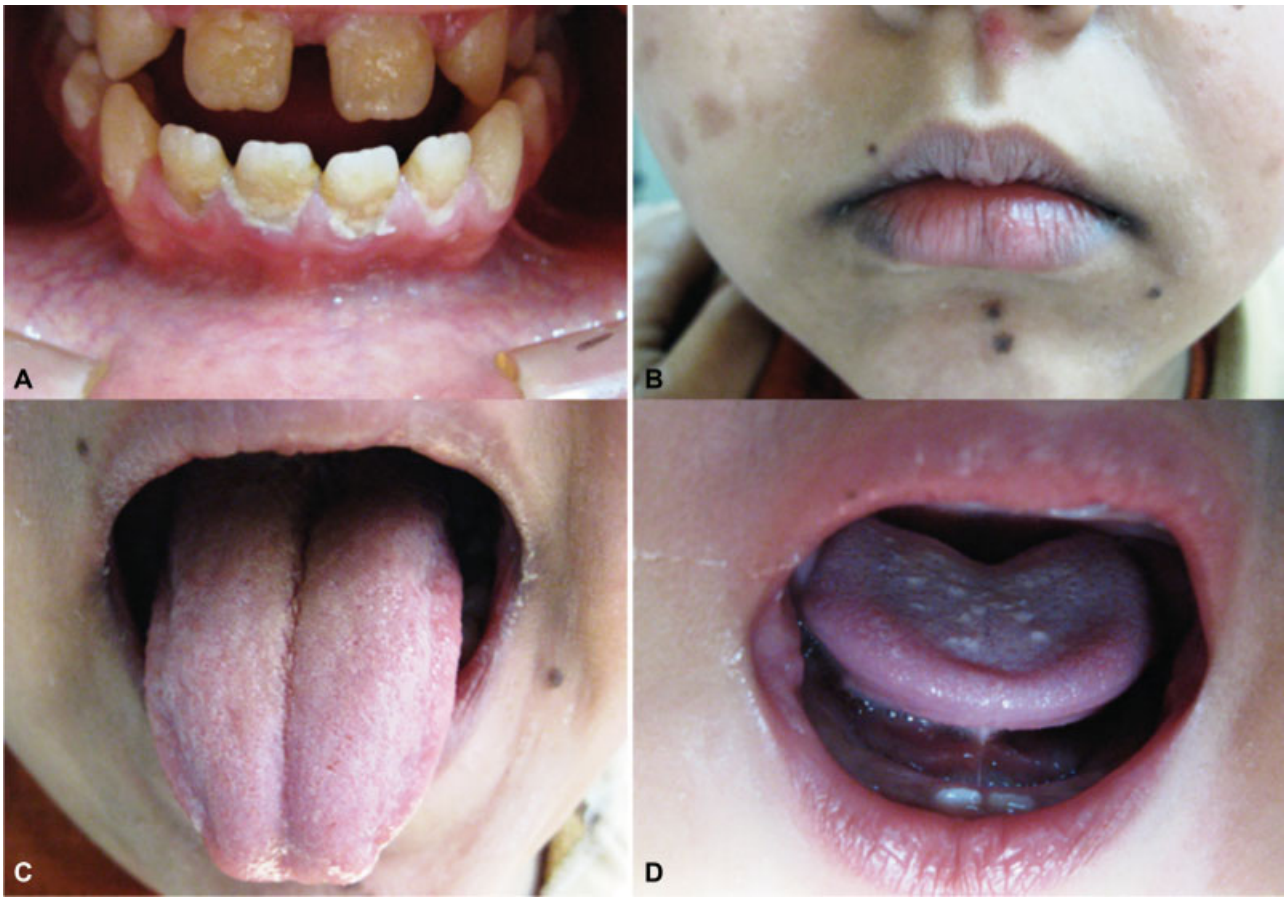


**Fig. 2** Oro-dental features of Prader-Willi syndrome. (**A**) Partial anodontia for upper lateral permanent incisors. (**B**) Triangular mouth, thick lips, and everted lower lip. (**C**) Median grooved tongue. (**D**) Partial ankyloglossia.

explain the normal bone density in 94.1% of our children with PWS.

Obesity and its complications are the foremost causes of morbidity and mortality in PWS.[4,30] Moreover, hyperphagia is a frequent symptom in patients with PWS and results in increased risk of metabolic and cardiovascular complications.[8,34] All our patients were overweight or obese; however, only 70% were committed to the nutritional program. They received laser acupuncture sessions beside the diet regulations for 6 months at least, to have 10 to 12 sessions. Their weight loss ranged from 4 to 8 kg, which emphasizes that control of food intake improves the health outcome in people with PWS.

Clinical PWS diagnostic criteria have been described by Holm et al[35]; however, Gunay-Aygun et al[14] published a set of PWS clinical diagnostic criteria considering the patients' age and described its scoring system. Applying this scoring system to our patients proved that 14 patients (82.3%) fulfilled the required diagnostic score during infancy (score of more than 5 points) (►**Table 1**). At the time of examination, sixteen children (94.1%) reached the required score for PWS diagnosis. Neonatal diagnosis of PWS has been attempted by several researchers.[36,37] Diagnosis of PWS in neonates may reduce complications of the disease and improve the quality of life of affected individuals. Hence, we emphasize application of PWS clinical diagnostic criteria and score to each neonate presenting with hypotonia and feeding difficulty. If the scoring fulfills the criteria for PWS diagnosis then performing cytogenetic analysis is essential, to rule out PWLS and confirm the diagnosis of PWS in around 70% of patients by standard karyotype and FISH analysis. The PCR-based methylation test (PBMT) for amplification of 15q11-q13 region is applied to confirm the diagnosis of most of the other 30% of patients.

In conclusion, early diagnosis of PWS during neonatal and infantile period is emphasized to allow implementation of proper management at an early stage, hence improving growth, development, and prognosis. The role of cytogenetic analysis is highlighted. Regular follow-up of diagnosed PWS patients by clinical examination, dental examination and nutritional evaluation is recommended to minimize the complications of the disease and improve the quality of life of PWS individuals.

### What's New

We report the clinical, oro-dental, cytogenetic and bone density findings of 17 PWS Egyptian patients. Some oro-dental features are documented for the first time. We also delineate a strategy for detection of PWS among infants.

### Ethical Approval

This research was reviewed and approved by the Research Ethics Committee at the National Research Centre

according to "World Medical Association Declaration of Helsinki" in 1995 (as revised in Seoul 2008) and written consents were obtained.

### Authors' Contributions

H.T.E.: concept and design of the study, N.H.: acquisition of data, I.M.: analysis and interpretation of data, A.E.A.: acquisition of data, M.I.M.: concept and design of the study, A.M.S.T.: drafting the article and revising it critically and final approval of the version.

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### Conflict of Interest

None declared.

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